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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,721	02/09/2004	Ralf Jockers	FRAV2003/0005USNP	9535

5487 7590 05/02/2008

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
05/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/774,721	JOCKERS ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-15,17,47, and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15,17,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 3/6/08 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 3/6/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 2/9/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 3/6/08, claims 12–15, 17, 47, and 48 are pending and currently under examination.

Claim Objections

Claim 14 is objected to because the claim contains text previously deleted from the claim without proper markings and the appropriate status identifier to show reinstatement of the text. In the amendment filed 8/7/07, the phrase "expressing an" was stricken from the claim and the phrase "incorporating the" was added. In the amendment filed 3/6/08, the status of claim 14 is

presented as "Previously presented", but the claim contains the phrase "expressing an", and the newly reinstated phrase is not underlined.

Correction is required in reply to this Action.

For purposes of this examination, claim 14 is examined as presented on 8/7/07, as it is believed that the inclusion of the phrase "expressing an" is simply an unintentional formatting or typographical error.

Claim 14 as presented on 8/7/07 reads as follows: A vector incorporating the oligonucleotide as claimed in one of claims 12 or 13.

Claim Rejections - 35 USC § 103—maintained

Claims 12–15, 17, 47, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailleul et al. (US Patent Application 2003/0166847); Agrawal and Tang (WO 94/01550); Taylor et al. (1999) *Drug Discovery Today* 4:562–567; Bennet et al. (US Patent 5,998,148); and Baracchini et al. (US Patent 5,801,154) for the reasons set forth in the Action mailed 9/7/2005.

Claims 15 and 48 were not previously included in the rejection. However, the Examiner notes that Bailleul et al. taught antisense oligonucleotides targeted to the LRGRP gene, pharmaceutical compositions thereof, and vectors and methods for expressing antisense oligonucleotides in cells (paragraphs 128-138). Therefore, one of skill would immediately recognize that Bailleul et al. necessarily also taught the vector-containing and cell-based compositions thereof used for and produced by such applications. Thus, the dependent claims 15 and 48 do not patentably distinguish the invention over the prior art cited herein.

Response to Arguments

In the reply filed 3/6/08, Applicants argue the applied references fail to teach or suggest all the claim limitations, stating the "two structural features" of the self-stabilized antisense oligonucleotides taught by Agrawal et al. are not embraced by the instant claims.

This argument is not persuasive because the instant claims clearly embrace hairpin and non-hairpin (i.e., bimolecular) RNA oligonucleotides. As explained in earlier Actions, Agrawal et al. taught materials and methods for making and using double stranded (hairpin) oligonucleotides of 8 to 50 nucleotides in length for inhibiting the expression of virtually any known gene in cells in vitro and in vivo. The two-structural features Applicant refers to are in fact the target hybridizing (antisense) and self-complementary (sense) regions essential to the activity of the self-stabilized oligonucleotides. Agrawal et al. taught that the self-stabilized oligonucleotide may comprise RNA, DNA, or both RNA and DNA (page 16). The constructs, which are preferably 8-50 nucleotides in length (pp. 9-10), may be fully base-paired, in much the same way a conventional short hairpin RNA is, as shown by Fig. 5 therein. See compound C, for example. Prior and post-filing art teaches that when such constructs are composed of RNA, they trigger RNAi-mediated silencing of the complementary mRNA. See, for example, Yu et al. (2002) *Proc. Natl. Acad. Sci.* 99:6047–6052, cited in the previous Action, stating and showing that short hairpin siRNAs can function like siRNA duplexes to inhibit gene expression in a sequence specific manner.

The combination of prior art cited herein suggests transfecting cells not only with the naked self-stabilized RNA constructs, but with vectors encoding such constructs, which would necessarily result in the expression of a short hairpin RNA. Therefore, the self-stabilized

constructs taught by Agrawal et al. meet all the structural limitations recited in the instant claims. The limitation "double-stranded RNA," recited in claim 13, does not distinguish over Agrawal et al. because hairpin RNAs are double stranded nonetheless.

Accordingly, the instant claims stand rejected as obvious over the instantly cited references.

Claim Rejections - 35 USC § 103—new

Claims 12-15, 17, 47, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailleul et al. (1997) *Nucleic Acids Res.* 25:2752-2758 in view of Tuschl et al. (US 2004/0259247 A1), Shi et al. (US 20030180756 A1), and Hannon (2002) *Nature* 418:244-251.

Bailleul et al. taught the mRNA (gene) sequence encoding human leptin receptor gene-related protein, OB-RGRP (Fig. 1). The sequence, deposited into GenBank as Accession No. Y12670 and available online as of 15 July 1997, is identical to instantly recited SEQ ID NO:21, as shown by the alignment below.

Bailleul et al. taught that OB-RGRP mRNA is expressed in several human tissues (page 2755). Bailleul et al. suggest OB-RGRP mRNA could encode a protein involved in leptin signaling (page 2757,right column, bottom). It is said that leptin and leptin receptor play key roles in the regulation of body weight (page 2752, left column, first sentence).

Bailleul et al. do not teach interfering RNA targeted to OB-RGRP mRNA, nor vectors thereof.

Tuschl et al. taught methods and materials for making and using short interfering RNAs (siRNAs) of 21 to 23 nucleotides in length for inhibiting the expression of any known gene in mammalian cells in vitro and in vivo for research and therapeutic purposes (see specification, pp.

1-16). It is taught siRNAs are useful for determining the function of a gene in a cell or organism (paragraph 29-30, for example). Also disclosed are compositions comprising said interfering RNAs (paragraphs 31-33). Exemplary embodiments describing and illustrating RNA interference in mammalian cells are also disclosed (Fig. 10, paragraph 146). Tuschl et al. suggest that short interfering RNAs may be expressed from vectors upon delivery into cells (paragraph 39).

Shi et al. taught plasmid and viral-based vectors for stably expressing short hairpin RNA in mammalian cells in vitro and in vivo for the RNAi-mediated inhibition of any known gene (pp. 1-9 and Fig. 1, for example). The method is expressly designed to facilitate the delivery and stable, endogenous expression of short interfering RNAs of the type taught by Tuschl et al. (page 1). Also disclosed are cells and compositions comprising said shRNA-expression vectors (paragraph 13, pages 18-20, and Examples 4-6, pages 22-25).

Accordingly, each of the elements of the instantly claimed invention are disclosed in the prior art. The prior art specifically recommends using siRNA and shRNA, transfected directly or expressed endogenously from vector constructs, as research tools to investigate gene function in mammalian cells. The shared properties and general utilities of siRNA and shRNA were explicitly taught by Hannon (2002) *Nature* 418:244-251, who stated in 2002 that "RNAi has evolved into a powerful tool for probing gene function" (page 250). Hannon goes on to state that Tuschl and colleagues showed that by using siRNA, RNAi could be extended to mammalian cells. Hannon states further that by employing stable expression constructs such as those disclosed by Shi et al., RNAi may be used to induce phenotypic changes in cells in vitro and in vivo (page 250). Thus, it is clear that RNAi was considered by the prior art to represent an

effective and generally applicable experimental tool for probing gene function and manipulating gene expression in cells and organisms.

Additionally, the sequence corresponding to SEQ ID NO:21---the mRNA encoding OB-RGRP---was known in the prior art. Moreover, there was reason to suspect its involvement in leptin signaling and body weight regulation. But even without such knowledge, there would have been implicit reason to investigate the biology of the sequence corresponding to SEQ ID NO:21, identified by Bailleul et al. as OB-RGRP, given that it is the normal desire of scientists to understand the biological role of each gene and translation product in the human genome. RNAi, a readily accessible and easily used method for silencing gene expression, was a well-established tool at the time of invention for investigating gene function.

It would therefore have been obvious to one of skill in the art at the time of invention to make and use siRNAs complementary to any known gene, including the OB-RGRP gene, SEQ ID NO:21, disclosed by Bailleul et al. One of skill would have been motivated to use the siRNAs to investigate the function of OB-RGRP in human cells and tissues, as generally directed by Tuschl et al. One of skill would have reasonably expected that the methods of Tuschl et al. and Shi et al. for making and using siRNAs and shRNA expression vectors could be applied to the study of OB-RGRP function, that the siRNAs and shRNA-expression vectors designed and prepared by such methods could be used to effectively inhibit OB-RGRP expression in cells in vitro and in vivo, and that such inhibition would yield information directly relevant to the function of said protein and gene. Given that the full-length sequence of OB-RGRP mRNA was known at the time of invention, and that Tuschl et al. and Shi et al. both taught the principles and methods for designing functional siRNAs (see siRNA User Guide in Tuschl et al., for example,

at paragraph 178-181), the skilled artisan would have had a reasonable expectation of success in making and using said siRNAs and shRNAs for inhibition of OB-RGRP.

Furthermore, all the claimed elements---the methods and materials for making and using siRNAs, shRNA expression vectors, host cells, and compositions thereof, and the OB-RGRP mRNA target sequence---were known in the prior art. One skilled in the art could have combined the elements by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results (i.e., inhibition of OB-RGRP expression) to one of ordinary skill in the art. *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

```
LOCUS       HSOBRGRP               1114 bp    mRNA    linear   PRI 09-SEP-2004
DEFINITION  Homo sapiens mRNA for leptin receptor gene-related protein.
ACCESSION   Y12670
VERSION     Y12670.1  GI:2266637
KEYWORDS    leptin receptor gene-related protein; OB-R gene related protein;
            OB-RGRP.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Bailleul,B., Akerblom,I. and Strosberg,A.D.
  TITLE     The leptin receptor promoter controls expression of a second
            distinct protein
  JOURNAL   Nucleic Acids Res. 25 (14), 2752-2758 (1997)
   PUBMED   9207021
REFERENCE   2  (bases 1 to 1114)
  AUTHORS   Bailleul,B.R.P.
  TITLE     Direct Submission
  JOURNAL   Submitted (17-APR-1997) B.R.P. Bailleul, UPR 0415 CNRS, 22 Rue
            Mechain, 75014 Paris, FRANCE
COMMENT     This is a splice variant from the leptin receptor locus but this
            variant encodes for a unrelated leptin receptor protein transcribed
            from one promoter of the leptin receptor locus.
FEATURES             Location/Qualifiers
     source          1. .1114
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /chromosome="1"
                     /map="1p32"
                     /dev_stage="adult"
     gene            1. .1114
                     /gene="OB-RGRP"
     mRNA            join(1114)
                     /gene="OB-RGRP"
     exon            1114
                     /gene="OB-RGRP"
                     /number=4
ORIGIN
```

Query Match **100.0%**; Score 1114; DB 5; Length 1114;
Best Local Similarity 100.0%; Pred. No. 0;
Matches 1114; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 GTCTGGCTTGGGCAGGCTGCCCGGGCCGTGGCAGGAAGCCGGAAGCAGCCGCGGCCCCAG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GTCTGGCTTGGGCAGGCTGCCCGGGCCGTGGCAGGAAGCCGGAAGCAGCCGCGGCCCCAG 60

Qy         61 TTCGGGAGACATGGCGGGCGTTAAAGCTCTCGTGGCATTATCCTTCAGTGGGGCTATTGG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TTCGGGAGACATGGCGGGCGTTAAAGCTCTCGTGGCATTATCCTTCAGTGGGGCTATTGG 120

Qy        121 ACTGACTTTTCTTATGCTGGGATGTGCCTTAGAGGATTATGGCGTTTACTGGCCCTTATT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 ACTGACTTTTCTTATGCTGGGATGTGCCTTAGAGGATTATGGCGTTTACTGGCCCTTATT 180

Qy        181 CGTCCTGATTTTCCACGCCATCTCCCCCATCCCCCATTTCATTGCCAAAAGAGTCACCTA 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 CGTCCTGATTTTCCACGCCATCTCCCCCATCCCCCATTTCATTGCCAAAAGAGTCACCTA 240

Qy        241 TGACTCAGATGCAACCAGTAGTGCCTGTCGGGAACTGGCATATTTCTTCACTACTGGAAT 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 TGACTCAGATGCAACCAGTAGTGCCTGTCGGGAACTGGCATATTTCTTCACTACTGGAAT 300

Qy        301 TGTTGTTTCTGCCTTTGGATTTCCTGTTATTCTTGCTCGTGTGGCTGTGATCAAATGGGG 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 TGTTGTTTCTGCCTTTGGATTTCCTGTTATTCTTGCTCGTGTGGCTGTGATCAAATGGGG 360

Qy        361 AGCCTGCGGCCTTGTGTTGGCAGGCAATGCAGTCATTTTCCTTACAATTCAAGGGTTTTT 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 AGCCTGCGGCCTTGTGTTGGCAGGCAATGCAGTCATTTTCCTTACAATTCAAGGGTTTTT 420

Qy        421 CCTTATATTTGGAAGAGGAGATGATTTTAGCTGGGAGCAGTGGTAGCACTTTATTCTGAT 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 CCTTATATTTGGAAGAGGAGATGATTTTAGCTGGGAGCAGTGGTAGCACTTTATTCTGAT 480

Qy        481 TACAGTGCATTGAATTTCTTAGAACTCATACTATCTGTATACATGTGCACATGCGGCATT 540
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Db        481 TACAGTGCATTGAATTTCTTAGAACTCATACTATCTGTATACATGTGCACATGCGGCATT 540

Qy        541 TTACTATGAAATTTAATATGCTGGGTTTTTTAATACCTTTATATATCATGTTCACTTTAA 600
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Db        541 TTACTATGAAATTTAATATGCTGGGTTTTTTAATACCTTTATATATCATGTTCACTTTAA 600

Qy        601 GAAAGACTTCATAAGTAGGAGATGAGTTTTATTCTCAGCAAATAGACCTGTCAAATTTAG 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 GAAAGACTTCATAAGTAGGAGATGAGTTTTATTCTCAGCAAATAGACCTGTCAAATTTAG 660

Qy        661 ATTATGTTACTCAAATTATGTTACTTGTTTGGCTGTTCATGTAGTCACGGTGCTCTCAGA 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy        721 AAATATATTAACGCAGTCTTGTAGGCAGCTGCCACCTTATGCAGTGCATCGAAACCTTTT 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 AAATATATTAACGCAGTCTTGTAGGCAGCTGCCACCTTATGCAGTGCATCGAAACCTTTT 780

Qy        781 GCTTGGGGATGTGCTTGGAGAGGCAGATAACGCTGAAGCAGGCCTCTCATGACCCAGGAA 840
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Db        781 GCTTGGGGATGTGCTTGGAGAGGCAGATAACGCTGAAGCAGGCCTCTCATGACCCAGGAA 840

Qy        841 GGCCGGGGTGGATCCCTCTTTGTGTTGTAGTCCATGCTATTAAAAGTGTGGCCCACAGAC 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 GGCCGGGGTGGATCCCTCTTTGTGTTGTAGTCCATGCTATTAAAAGTGTGGCCCACAGAC 900

Qy        901 CAAGAGCCTCAACATTTCCTAGAGCCTTATTAGAAATGCAGAATCTGAAGCCCCACTCTG 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 CAAGAGCCTCAACATTTCCTAGAGCCTTATTAGAAATGCAGAATCTGAAGCCCCACTCTG 960

Qy        961 GACCCAGGACATTTTGATGAGATCCAAAGGAGTTGTATGCACATGAAAGTTTGAGAAGCA 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        961 GACCCAGGACATTTTGATGAGATCCAAAGGAGTTGTATGCACATGAAAGTTTGAGAAGCA 1020

Qy       1021 TCATCATAGAGAAGTAAACATCACACCCAACTTCCTTATCTTTCCAGTGGCTAAACCACT 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1021 TCATCATAGAGAAGTAAACATCACACCCAACTTCCTTATCTTTCCAGTGGCTAAACCACT 1080

Qy       1081 TAACCTCTCTGGGTGTTACCTGCTCATTTGTTTA 1114
              |||||||||||||||||||||||||||||||||
Db       1081 TAACCTCTCTGGGTGTTACCTGCTCATTTGTTTA 1114
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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
April 29, 2008